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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,621	TAYLOR ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/30/02+5/29/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-17 have been canceled. Claims 18-50 are pending and examined on the merits.

Priority

2. Acknowledgment is made of applicant's claim to an earlier effective filing date via the co-pending applications of 60/181,143, 09/392,500, 60/099,782 and 60/123,786. Upon review of all the aforesaid applications it is noted that only 60/181,143 provides support for the instant invention of inhibiting or suppressing microbial or viral replication in a mammal and a method of treating septic shock in an animal, because the other applications described only methods of treating and diagnosing cancer. Accordingly, the instant claims will receive the effective priority date of February 8, 2000.

Claim Objections

3. Claims 48 and 50 are objected to because of the following informalities:

a. Claim 50 consists of more than one sentence and repeats species of the first sentence within the second sentence,

b. Claim 50, line 8 has a typographical error in the spelling of pseudotuberculosis.

c. Claim 48 has a typographical error in the spelling of "coronavirus"

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear if IgM is required to be bound to a virus.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 23, 28-31 and claims 39-44, in part and 46-50 in part are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claim 20 is drawn to a method for inhibiting or suppressing viral replication in an animal, said method comprising administering to said animal a therapeutically effective amount of one or more nucleic acid sequences encoding one or more anti-C3b(i) antibodies. Claim 28 embodies the method of claim 20 further comprising administering one or more nucleic acid sequences encoding one or more complement components. Claim 29 embodies the method of claim 20 or 28 further comprising administering one or more nucleic acid sequences encoding one or more antibodies immunospecific for one or more viral antigens.

Claim 23 is drawn to a method for inhibiting or suppressing microbial replication in an animal, said method comprising administering to said animal a therapeutically effective amount of one or more nucleic acid sequences encoding one or more anti-C3b(i) antibodies. Claim 30 embodies the method of claim 23 further comprising administering one or more nucleic acid sequences encoding one or more complement components. Claim 31 embodies the method of claim 23 or 30 further comprising administering one or more nucleic acid sequences encoding one or more antibodies immunospecific for one or more microbial antigens.

Claims 39 and 40 embody claims 20 and 23 in part, wherein the animal is a mammal or a human, respectively. Claim 41 embodies claim 20 in part wherein at least one of the anti-C3b(i) antibodies is immunospecific for C3b(i) linked to IgM or IgG bound to a virus. Claim 42 embodies claim 20 in part wherein at least one of the anti-C3b(i) antibodies is immunospecific for C3b(i) linked to a viral antigen. Claim 46 embodies the method of claim 42 wherein at least one of the antigens is HIV gp120 or RSV F glycoprotein. Claim 48 embodies claim 20 in part

wherein the viral infection is caused by a retrovirus, a herpes virus, an arena virus, a paramyxovirus, an adenovirus, a bunyavirus, a coronavirus, filovirus, flavivirus, hepadnavirus, orthomyovirus, papovavirus, picornavirus, poxvirus, reovirus, togavirus or a rhabdovirus.

Claim 43 embodies claim 23 in part, wherein at least one of the anti-C3b(i) antibodies is immunospecific for C3b(i) linked to IgM or IgG bound to a microbe. Claim 44 embodies claim 23 in part, wherein at least one of the anti-C3b(i) antibodies is immunospecific for C3b(i) linked to a microbial antigen. Claim 47 embodies the method of claim 44 wherein at least one of the microbial antigens is LPS. Claim 49 embodies claim 23 in part wherein the microbial infection is a yeast, fungal, protozoan or bacterial infection. Claim 50 embodies the method of claim 49 wherein the bacterial infection is caused by the listed bacterial species.

(A) As drawn to nucleic acid sequences encoding antibodies.

The instant method claims require the administration of nucleic acid sequences to a mammal which would encode within the cells of said mammal antibodies which bind to C3b(i), and one or more antibodies which are immunospecific for a multitude or viral and microbial antigens. The claims encompass the administration of nucleic acid sequences encoding whole antibodies comprising both light and heavy chains as well as single stranded antibodies. The art teaches that it is necessary to know the amino acid sequence of a CDR regions for any antibody, be it a multi-chain antibody or a single chain antibody in order to design a nucleic acid encoding said antibody (Jones et al., Advanced Drug Delivery Reviews 1998, page 154, column 1, lines18-26, and page 160, lines 24-25). The specification does not teach the amino acid sequence of the CDR region of any antibody. One of skill in the art would be subject to undue experimentation first to determine the amino acid sequence of an antibody which binds to C3b(i), as well as the amino acid sequence of the antibodies which bind to the multitude of microbial and viral antigens claimed in order to make the nucleic acid sequence required for the instant claims.

(B) As drawn to the administration of a nucleic acid sequence in vivo

The instant claims require that a therapeutically effective amount of the nucleic acids encoding the above antibodies be delivered in vivo to an animal in need of suppression of viral or microbial replication. It is noted that the genus of microbes and viral agents encompassed by the claims includes microbes and viruses that infect a multitude of different sites within the body.

For instance, N gonorrhea infects the urogenital tract, C diphtheria infects the mucous membranes and skin, K pneumoniae produces both a urinary and respiratory infection and H influenzae infects the mucous membranes. The specification provides no guidance as to how to target the administered nucleic acids to the tissue or organ which is infected. The specification provides no guidance as to the level and duration of expression which would be necessary to induce a therapeutically effective dose. The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or vectors comprising said nucleic acids. The state of the art as of the priority date sought for the instant application is that in vivo delivery of nucleic acids is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression within cells which are expressing the gene, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the nucleic acid, the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically with respect to the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

Orkin et al ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) state that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of nucleic acids. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been

experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the infected tissue type. The specification does not remedy any of the deficiencies or the prior art with regard to the delivery of nucleic acids in vivo to produce an efficacious effect Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims drawn to the administration of a nucleic acid.

7. Claims 20, 23, 28-31, and claims 39-44, in part and 46-50 in part are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

The instant claims are method claims reliant on the identify of nucleic acid sequences which encode anti-C3b(i) antibodies, and antibodies which bind to viral and microbial antigens. Thus the claims encompass a genus of nucleic acids which encode antibodies which bind to C3b(i) and a genus of nucleic acids which encode a plethora of viral and microbial antigens. The specification does not teach the primary amino acid sequence of any of the antibodies, thus the instant claims rely on products described only by their function of encoding anti-C3b(i) antibodies and anti-viral and anti-microbial antibodies but the specific structure of the encoded antibody is not taught, and neither is a partial structure of the CDR regions or variable chains of said encoded antibody.

The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

In the instant specification the nucleic acids are described only by function and therefore fails to adequately describe the products on which the instant methods claims are based. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed genus on which the method claims rely.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 18, 19, 38, 39, 40, 42, 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al (US 5,470,570) in view of the abstract of the abstract of Stoiber et al (Immunobiology, 1995, Vol. 193, pp. 98-113).

Claim 18 is drawn to a method for inhibiting viral replication in an animal, said method comprising administering to the animal a therapeutically effective amount of one or more ani-C3b(i) antibodies.

Claim 19 is drawn to a method for inhibiting viral replication in an animal, said method comprising administering to the animal a therapeutically effective amount of one or more ani-C3b(i) antibodies and one or more antibodies specific to one or more viral antigens.

Claim 38 embodies the methods of claims 18 or 19 in which at least one of the antibodies is conjugated to a therapeutic agent.

Claims 39 and 40 embody the methods of claims 18 and 19, wherein the animal is a mammal and a human, respectively.

Claim 42 embodies the method of claims 18 or 19 wherein at least one of the anti-C3b(i) antibodies is immunospecific for C3b(i) linked to a viral antigen. Claim 46 specifies that the viral antigen of claim 42 is gp120 of HIV. Claim 48 embodies the method of claim 18 or 19 wherein the viral infection is caused by a retrovirus.

Taylor et al teach a method of using franked red blood cells with specificity to an antigen such as HIV to clear free antigen from the blood of a human patient (column 7, lines 1-3), and a method of using franked red blood cells with specificity to C3b (column 7, lines 7-8). Taylor et al teach that the level of free HIV in the blood is the most cytopathic form of the virus (column 7, lines 55-58). It is noted that the specification defines C3b(i) as including C3b and its

fragments such as C3bi, C3b and C3d (page 7, lines 6-7) and antibodies which bind to C3b(i) as antibodies which bind to C3b-opsonized cells (page 7, lines 11-12). Taylor et al teach that RBCs can be franked with a cocktail of several heteropolymers which in addition to the binding of target antigen, can also bind to non-overlapping epitopes of CR1 which allows a small number of RBC to bind a larger number of antigen (column 2, lines 41-56). Taylor et al do not specifically teach franked red blood cells with cocktails of heteropolymers specific to both an HIV antigen and C3b on target HIV.

The abstract of The abstract of Stoiber et al teaches that C3b reacts with the gp120 envelope protein of HIV-1 (abstract).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to frank red blood cells with a cocktail of heteropolymers which comprised anti-CR1 antibodies which bound to different epitopes of CR1, conjugated to anti-C3b antibodies, and anti-C3b antibodies which bind to C3b attached to gp120 and to administer said franked red blood cells for the treatment of HIV infection, and it would have been an intrinsic property that the antibody would bind to C3b attached to gp120, because The abstract of Stoiber teaches that C3b reacts with gp120. One of skill in the art would have been motivated to do so by the teachings of The abstract of Stoiber et al on the deposition of C3b on HIV-1 and the specific interaction of C3b with gp120. The franked red blood cells would fulfill the specific embodiments of claim 38 because the therapeutic agent would be the erythrocyte.

11. Claims 18, 19, 34, 38, 39, 40-42, 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al and the abstract of Stoiber et al as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48 above, and further in view of Nilsson et al (Molecular Immunology, 1987, vol. 24, pp. 487-494).

Claim 34 specifies that the methods of claims 18 and 19, wherein at least one of the anti-C3b(i) antibodies is a monoclonal antibody.

Claim 41 embodies the method of claims 18 or 19 wherein at least one of the antibodies is immunospecific for C3bi linked to IgM or IgG antibody bound to a virus.

Neilsson et al teach monoclonal anti-C3(D) antibodies which bind exclusively to neoantigenic eptiopes found in physiologically bound C3 and are thus reagents for the detection

of immune complex bound C3b and iC3b (Table 3 and page 493, second column, lines 13-16 and lines 35-39).

It would have been prima facie obvious at the time the invetion was made to use the use the monoclonal anti-C3(d) antibodies as taught by Neilsson et al as part of the heteropolymer rendered obvious by the combination of Taylor et al and The abstract of Stoiber et al. One of skill in the art would have been motivated to do so by the teachings of Neilsson et al on the ability of said anti-C3(D) antibodies to bind to physiologically bound forms of C3. One of skill in the art would have been motivated to include such an antibody in order to eliminate binding to C3 or C3 fragments which were not physiologically bound to the HIV virus.

12. Claims 18, 19, 34, 35, 38, 39, 40-42, 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al and the abstract of Stoiber et al and Nilsson et al as applied to claims 18, 19, 34, 38, 39, 40-42, 46 and 48 above, and further in view of Queen et al (5,530,101).

Claim 35 embodies the monoclonal antibody of claim 34 which is human or humanized.

Taylor et al teach that available human monoclonal antibodies can be used to prepare the heteropolymers to avoid host immune response (column 7, lines 46-48). Nilsson et al teach a monoclonal antibody which specifically binds to C3 fragments physiologically bound to substrate. None of the combined references specifically teach a human or humanized anti-C3b antibody.

Queen et al teach that the immune response mounted by a patient against a non-human antibody can be quite strong, essentially eliminating the therapeutic effect of the antibody after an initial treatment (column 1,lines 41-47). Queen et al teach a method for making humanized antibodies specifically reactive with strong affinity to a predetermined antigen which remain substantially non-immunogenic in humans (column 2, lines 25-31).

It would have been prima facie obvious at the time the claimed invention was made to make the heteropolymer rendered obvious by the combination of Taylor et al and The abstract of Stoiber et al with a humanized anti-C3(D) antibody as taught by Nilsson et al. One of skill in the art would have been motivated to do so by the suggestion of Taylor et al that human antibodies

be utilitized in the heteropolymer and the teachings of Queen et al on the humanization of antibodies to decrease their immunogenicity in vivo while retaining antigen affinity.

13. Claims 18, 19, 24-26, 34, 38, 39, 40, 42, 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al (US 5,470,570) and the abstract of Stoiber et al (Immunobiology, 1995, Vol. 193, pp. 98-113) as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48 above, and further in view of Montefiori et al (Journal of Infectious Diseases, 1994, Vol. 170, pp. 429-430).

Claims 24 and 25 embody the methods of claims 18 and 19 further comprising administering IgG enriched plasma and IgM enriched plasma. Claim 26 embodies the method of claim 24 further comprising administering IgM enriched plasma.

Montefiori et al teach that complement alone targeted HIV-1 to red blood cells but envelope specific antibodies increased this effect (abstract, lines 7-10). Montefiori et al teach that the envelope-specific antibodies were obtained from gp-160 immunized volunteers (page 431, second column, lines 6-8). It is reasonable to conclude that the sera from the vaccinated volunteers harbored both IgG and IgM anti-gp160 antibodies.

It would have been prima facie obvious to one of skill in the art at the time the invetion was made to administer envelope-specific antibodies in addition to the franked erythrocytes rendered obvious by the combination of Taylor et al and The abstract of Stoiber et al. One of skill in the art would have been motivated to do so by the teachings of Montefiori et al on the increase of binding to the CR1 receptor by opsonized envelope specific antibodies and complement. One of skill in the art would have been motivated to increase the binding of free HIV-1 to the CR1 receptor in order to target the free HIV-1 to the reticulo-endothelial system as taught by Taylor et al.

14. Claims 18, 19, 34, 38, 39, 40, 42, 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al and the abstract of Stoiber et al as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48 above, and further in view of Peng et al (Clinical and Diagnostic Laboratory Immunology, 1996, Vol. 3, pp. 128-131).

Claim 27 embodies the method of claims 18 and 19 further comprising administering one or more complement components.

The combination of Taylor et al and The abstract of Stoiber et al render obvious the limitations of claims 18, 19, 34, 39, 40, 42, 46 and 48 for the reasons set forth above. Neither of the references teaches the administration of one or more complement components.

Peng et al teaches that HIV infection leads to complement deficient immune complexes (page 130, second column, last paragraph).

It would have been prima facie obvious at the time the claimed invetion was made to administer complement components in conjunction with the franked red blood cells rendered obvious by the combined teachings of Taylor et al and The abstract of Stoiber et al. One of skill in the art would be motivated to do so in order to provide adequate C3b deposition on free HIV-1, so that the heteropolymers comprising the anti-C3bi antibodies on the franked red blood cells will bind multiple HIV viruses.

15. Claims 18, 19, 33, 36-39, 40, 42, 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al and the abstract of Stoiber et al as applied to claims 18, 19, 38, 39, 40, 42, 46 and 48 above, and further in view of Lenz et al (US 6,060,285).

Claim 33 is drawn to the method of claim 18 or 19 wherein at least one of the anti-C3b(i) antibodies is a bispecific antibody which binds to C3b(i) and a effector cell receptor or antigen. Claim 36 embodies in part the method of claim 33 wherein the effector cell is a erythrocyte. Claim 37 embodies in part the method of claim 33 wherein the antigen is CR1.

The combination of Taylor et al and The abstract of Stoiber et al render obvious the instant claims wherein the heteropolymer consists of anti-CR1 antibodies which bind to non-overlapping eptiopes of CR1 conjugated to anti-C3b antibodies for the reasons set forth above. Neither Taylor et al nor The abstract of Stoiber et al teach bi-specific antibodies which bind CR1 and C3b.

Lenz et al teach bispecific antibodies which have two different antigen binding sites directed towards two different epitopes useful for the therapy of diseases. Lenz et al teach an example of a bispecific antibody having one antigen binding site directed towards a T-cell surface antigen and the second antigen binding site is directed towards an antigenic determinant

of a virus column 1, lines 7-18). Lenz et al teach that the bi-specific antibodies are especially suitable for diseases caused by viruses and that the therapist has a wide field from which he can choose the respective best combination of the two antigenic determinants (column 4, lines 5-9). Lenz et al teach a method for making the bi-specific antibodies which is less complicated than a method of chemically conjugating two different antibodies (column 1, lines 21-27), such as that used for the production of the heteropolymer taught by Taylor et al.

It would have been prima facie obvious at the time the claimed invention was made to substitute bi-specific antibodies which bind to both the CR1 receptor of a red blood cell and C3b on the target HIV-1 viron in the method rendered obvious by the combination of Taylor et al and The abstract of Stoiber et al. One of skill in the art would have been motivated to do so by the teachings of Lenz et al on the ease of making such bi-specific antibodies relative to chemically conjugating two different antibodies and the high yield of bi-specific antibodies attained through the method of Lenz et al.

16. Claims 18, 24, 34, 38, 39, 40 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al (US 5,470,570) in view of Ebenbichler et al (Journal of Experimental Medicine, 1991, Vol. 174, pp. 1417-1424) and Nilsson et al (Molecular Immunology, 1987, vol. 24, pp. 487-494).

Taylor et al teach a method of using a franked red blood cells with specificity to an antigen such as HIV to clear free antigen from the blood of a human patient (column 7, lines 1-3), and a method of using franked red blood cells with specificity to C3b (column 7, lines 7-8). Taylor et al teach that the level of free HIV in the blood is the most cyopathic form of the virus (column 7, lines 55-58). It is noted that the specification defines C3b(i) as including C3b and its fragments such as C3bi, C3b and C3d (page 7, lines 6-7) and antibodies which bind to C3b(i) as antibodies which bind to C3b-opsonized cells (page 7, lines 11-12). Taylor et al teach that RBCs can be franked with a cocktail of several heteropolymers which in addition to the binding of target antigen, can also bind to non-overlapping epitopes of CR1 which allows a small number of RBC to bind a larger number of antigen (column 2, lines 41-56). Taylor et al do not specifically teach franked red blood cells with cocktails of heteropolymers specific to both an HIV antigen and C3b on target HIV.

Ebenbichler et al teach that retroviruses isolated from avian, feline, murine and simian sources direct the induction of the classical complement pathway, whereas cells infected with said retroviruses activate the alternative pathway (page 1417, first column, lines 1-4 and lines 11-15). Ebenbichler et al teach the deposition of C3b and C3d on HIV infected cells (page 1417, first column, lines 13-14).

Neilsson et al teach monoclonal anti-C3 antibodies (D) which bind exclusively to neoantigenic eptiopes found in physiologically bound C3 and are thus reagents for the detection of immune complex bound C3b and iC3b (Table 3 and page 493, second column, lines 13-16 and lines 35-39).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to frank red blood cells with a cocktail of heteropolymers which comprised anti-CR1 antibodies which bound to different epitopes of CR1, wherein said anti-CR1 antibodies are conjugated to the anti-C3(D) antibody taught by Neilsson et al and to administer said franked red blood cells for the treatment of retrovirus infections. One of skill in the art would have been motivated to do so by the teachings of Ebenbichler et al on the activation of complement by both free retroviruses and retrovirus-infected cells and the deposition of C3 onto retrovirus infected cells. One of skill in the art would recognize that the C3b and/or the C3bi would be specific to a retrovirus-infected cell versus a non-retrovirus infected cells and therefore C3b or C3bi can be used as a target antigen for said cells.

17. Claims18, 24, 33, 34, 36-40 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al and Ebenbichler et al and Nilsson et al as applied to claims 18, 24, 34, 38, 39, 40 and 48 above, and further in view of Lenz et al (US 6,060,285).

Claim 33 embodies the method of claim 18 wherein at least one of the anti-C3bi antibodies is a bispecific antibody which is mmunospecific for C3bi and an effector cell antigen. Claim 36 embodies the method of claim 33 in which the effector cell is a monocyte, macrophage, dendritic cell, neutrophil, natural killer cell or erythrocyte. Claim 37 embodies the method of claim 33 in which the antigen is CR1, CR2, CR3, CR4, CD16, CD32, CD64 or CD89.

The combination of Taylor et al and Ebenbichler et al render obvious the instant claims wherein the heteropolymer consists of anti-CR1 antibodies which bind to non-overlapping

eptiopes of CR1 conjugated to anti-C3(D) antibodies for the reasons set forth above. Neither Taylor et al nor Ebenbichler et al teach bi-specific antibodies which bind CR1 and C3(D).

Lenz et al teach bispecific antibodies which have two different antigen binding sites directed towards two different epitopes useful for the therapy of diseases. Lenz et al teach an example of a bispecific antibody having one antigen binding site directed towards a T-cell surface antigen and the second antigen binding site is directed towards an antigenic determinant of a virus column 1, lines 7-18). Lenz et al teach that the bi-specific antibodies are especially suitable for diseases caused by viruses and that the therapist has a wide field from which he can choose the respective best combination of the two antigenic determinants (column 4, lines 5-9). Lenz et al teach a method for making the bi-specific antibodies which is less complicated than a method of chemically conjugating two different antibodies (column 1, lines 21-27), such as that used for the production of the heteropolymer taught by Taylor et al.

It would have been prima facie obvious at the time the claimed invention was made to substitute bi-specific antibodies which bind to both the CR1 receptor of a red blood cell and C3(D) on the target free retroviruses or cells infected with retroviruses in the method rendered obvious by the combination of Taylor et al and Ebenbichler et al. One of skill in the art would have been motivated to do so by the teachings of Lenz et al on the ease of making such bi-specific antibodies relative to chemically conjugating two different antibodies and the high yield of bi-specific antibodies attained through the method of Lenz et al.

18. Claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanger et al (EP 255, 249) as evidenced by Abbas et al (Cellular and Molecular Immunology (text), 1991, pp. 398-400) in view of Newman et al (Journal of Experimental Medicine, 1985, Vol. 161, pp. 1414-1431) and Neilsson et al (Molecular Immunology, 1987, vol. 24, pp. 487-494) as evidenced by Vogel et al (Infections and Immunity, 1997, Vol. 65, pp. 4022-4029).

Claim 21 is drawn to a method for inhibiting microbial replication in an animal, said method comprising administering to the animal a therapeutically effective amount of one or more ani-C3b(i) antibodies. Claim 33 embodies the method of claims 21 wherein at least one of the anti-C3bi antibodies is a bispecific antibody which is immunospecific for C3bi and an

effector cell receptor antigen. Claim 34 embodies the method of claims 21 wherein at least one of the C3bi antibodies is a monoclonal antibody. Claim 36 embodies the methods of claims 33 wherein the effector cell is a lymphocyte, monocyte, macrophage, dendritic cell, neutrophil, natural killer or erythrocyte. Claim 37 embodies the method of claim 33 in which the antigen is CR1, CR2, CR3, CR4, CD16, CD32, CD64 or CD89. Claim 38 embodies the methods of claim 21 or 32 in which at least one of the C3bi antibodies is conjugated to a therapeutic agent. Claims 39 and 40 embody the method of claim 20, wherein the animal is a mammal and a human, respectively. Claim 43 embodies the methods of claim 21 wherein at least one of the anti-C3bi antibodies is immunospecific for C3bi linked to IgM or IgG bound to a microbe. Claim 44 embodies the method of claim of claim 21 wherein at least one of the anti-C3bi antibodies is immunospecific for C3bi linked to a microbial antigen. Claim 47 embodies the method of claim 44 in which at least one of the microbial antigens is LPS. Claim 49 embodies the methods of claim 21 in which the microbial infection is a bacterial infection. Claim 50 embodies the method of claim 49 wherein the bacterial infection is caused by S pyrogenes, S pnemoniae, H influenza, S aureus and E coli.

Fanger et al teach a method for eliminating undesirable target cells which include microorganisms such as bacteria and viruses comprising administering a bi-specific antibody which binds to the Fc receptors of effector cells (abstract, lines 8-11, page 5, lines 49-50 and page 8, lines 49-50). Fanger et al teach that the target cell can be a cancer cell or other cell whose elimination would be beneficial to the host, wherein target cell specificity of the bifunctional antibody or the hetero-antibody is derived from a targeting antibody i.e., an antibody specific for a target cell-associated or target cell-specific antigen (page 3, lines 29-32). Fanger et al teach bifunctional antibodies or heteroantibodies for the targeting of effector cells in which the antibodies have dual antigen binding specificity -one specificity for the Fc receptor and one specificity for an epitope of the target cell (page 5, lines 8-10). The teachings of Fanger et al fulfill the specific embodiments of claim 37 because the Fc receptors on the surface of macrophage and monocytes are gamma, I, II and III, which are the same as CD64, CD32 and CD16, respectively, as evidenced by the "Common Synonyms" provided by the appendix of Abbas et al. Fanger et al teach that the Fc receptor specificity mediates linkage to the effector cell through a known cytotoxic trigger molecule and that the target cell specificity provides for

recognition and binding to the target cell (page 5, lines 10-12). Fanger et al teach that the use of the Fc specific antibody of this invention provides for attachment of the targeting antibody to monocyte effector cells by a linkage which is not disrupted by physiological levels of immunoglobulin G encountered in vivo allowing for the administration of the targeted effector cells without loss of effector cell specificity due to IgG competition for Fc receptor sites (page 3, lines 32-37). Fanger et al teach that the antibody binds the high affinity (p72) Fc receptor (FcRI) for human IgG without being blocked by human IgG and that preferred anti-FcRI receptor antibody has the following characteristics: a. the antibody reacts specifically with the high affinity Fc receptor; b. the antibody reacts with the receptor through its antigen combining region independent of its Fc portion; c. the antibody reacts with an epitope of FcRI which is distinct from the Fc (or ligand binding) site of the receptor; and d. the antibody binds ligand (Fc) occupied receptor (page 4, lines 9-16). Fanger et al teach that effector cells for targeting include human leukocytes, preferably macrophages and monocytes, IFN-gamma activated neutrophils, and possibly IFN-gamma activated natural killer (NK) cells and eosinophils (page 5, lines 52-55). Fanger et al does not teach bi-specific antibodies which target C3 or C3bi on bacteria.

Newman et al teach that E coli, S pnemoniae, S pyrogenes, S aureus and H influenza all activate the alternative complement pathway and require phagocytosis for removal from the host. Newman et al teach that when the aforesaid bacteria were incubated in serum, between 16-28% of the C3b was converted to C3bi (page 1426, lines 1-6 of the third paragraph). Thus, S pnemoniae, S pyrogenes, S aureus and H influenza have a mixture of C3b and C3bi on their surfaces.

Neilsson et al teach monoclonal anti-C3 antibodies (D) which bind exclusively to neoantigenic eptiopes found in physiologically bound C3 and are thus reagents for the detection of immune complex bound C3b and iC3b (Table 3 and page 493, second column, lines 13-16 and lines 35-39) and fulfill the specific embodiments of claims 43 and 44 because the physiologically bound C3b and C3bi to which the anti-C3(D) antibodies bind would include C3b and C3bi attached to a microbial antigen as well as C3b and C3bi attached to IgM on the surface of the bacterium. Neilsson et al fulfill the specific embodiments of claim 47 because the physiologically bound C3b and C3bi is linked to the surface structure of encapsulated bacteria which comprises LPS, as evidenced by Vogel et al (abstract, lines 7-9).

It would have been prima facie obvious at the time the invention was made to use the anti-C3 (D) antibodies of Neilsson et al in the method of eliminating bacteria as taught by Fanger et al. One of skill in the art would have been motivated to do so by the teachings of Newman et al regarding the deposition of C3 b on the surface of E coli, S pnemoniae, S pyrogenes, S aureus and H influenza and the subsequent degradation of same of the C3b to C3bi, and the teachings of Neilsson et al on the anti-C3(D) antibodies which bind to both physiologically bound C3b and C3bi

19. Claims 21, 33, 34, 36-40, 43, 44, 47, 49, 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanger et al and Newman et al and Neilsson et al and Vogel et al as applied to claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 above, and further in view of and Todd (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1-2) and Fang et al (Journal of Immunology, 1998, Vol. 160, pp. 5273-5279) and Abbas et al (Cellular and Molecular Immunology, (text), 1991, page 273) and the abstract of Pulford et al (Int Immunol, 1990, Vol. 2, pp. 973-980). Claim 37 embodies the method of claim 33 in which the antigen is CR1, CR2, CR3, CR4, CD16, CD32, CD64 or CD89.

The combination of Fanger et al as evidence by Abbas et al and Newman et al and Neilsson et al render obvious the instant claims wherein the effector cell antigen to which the bispecific or heterospecific antibodies bind is CD16, CD32 and CD64 for the reasons set forth above. Fanger et al teach that effector cells for targeting include human leukocytes, preferably macrophages and monocytes, IFN-gamma activated neutrophils, and possibly IFN-gamma activated natural killer (NK) cells and eosinophils (page 5, lines 52-55). The combination does not specifically teach the effector cell antigens of CR4 or CD89.

Fang et al teach that CR1 is expressed on the surface of erythrocytes, macrophage, neutrophils, B-cells, follicular dendritic cells and a subset of T-cells (page 5273, second column. lines 1-4). Fang et al teach that CR2 is expressed on the surface of follicular dendritic cells and some T-cells (page 5273, second column, lines 18-19).

Todd teaches that CR3 is expressed on the surface of mononuclear phagocytes and natural killer cells (page 1, column 2, lines 4-7).

Abbas et al identify CR4 as found on neutrophils and monocytes.

The abstract of Pulford et al teaches that CD68 is expressed by macrophage and monocytes.

It would have been prima facie obvious at the time the claimed invetion was made to use the method rendered obvious by the combination of Fanger et al and Newman et al and Neilsson et al to target leukocytes, such as macrophages and monocytes, neutrophils, or natural killer (NK) cells by means of bispecific antibodies or heteroantibodies which bind CR1, CR2, CR3, CR4, or CD68. One of skill in the art would have been motivated to do so by the teachings of Fang et al, Todd, Abbas et al or the abstract of Pulford et al which identifies the aforesaid antigens as present on leukocytes and the suggestion by Fanger et al that the effector cells could be human leukocytes.

20. Claims 21 24-27, 33, 34, 36-40, 43, 44, 47, 49, 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanger et al and Abbas et al and Newman et al and Neilsson et al and Vogel et al as applied to claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 above, and further in view of Quie (Scand J Infect Dis, 1971, suppl. 31, pp. 34-40).

Claim 24 embodies the method of claim 21 further comprising administering IgG enriched plasma. Claim 25 embodies the method of claim 21 further comprising administering IgM enriched plasma. Claim 26 embodies the method of claim 25 further comprising administering IgM enriched plasma. Claim 27 embodies the method of claim 21 further comprising administering one or more complement components.

The combination of Fanger et al as evidence by Abbas et al and Newman et al and Neilsson et al and Vogel et al render obvious the instant claims wherein the effector cell antigen to which the bispecific or heterospecific antibodies bind is CD16, CD32 and CD64 for the reasons set forth above. None of the aforesaid references specifically teaches the administration of IgG or IgM enriched plasma.

Quie teaches that IgG antibodies on the surface of microbes are efficient opsonins acting by attachment of the antibody Fc region to the Fc receptors on phagocytic cells and that IgM antibodies are efficient activators of complement on the surface of microbes and act indirectly as opsonins by fixing C3b which can then attach to C3b receptors on phagocytic cells (page 38, first column, lines 27-33). Quie et al teaches that the alternative pathway of complement activation is

critical for protection against septicemia as evidenced by the ability of virulent E coli, such as K-1 to resist activation of the alternative pathway and to result in the septic state (page 35, column 2, lines 13-19). Quie teaches that when specific antibodies are present, there is antibody mediated activation of the complement pathway via the classical pathway and C3b is deposited on the microbial surface in spite of the sialic acid on the E coli surface (page 35, second column, lines 31-36). Quie teaches that a clear separation between the classical pathway ad the alternative pathway is not possible because C3b activated by the classical pathway is part of C3b of the alternative pathway and both pathways may be antibody independnet or antibody dependent. (35, second column, lines 37-43).

It would have been prima facie obvious at the time the claimed invention was made to further administer IgG enriched and IgM enriched plasma and C3b molecules in addition to the bispecific or heterospecific antibodies rendered obvious by the teachings of Fanger et al as evidenced by Abbas et al and Newman et al and Neilsson et al. One of skill in the art would have been motivated to provide IgG enriched plasma to increase the phagocytosis of the microbial cells according to the teachings of Quie. One of skill in the art would have been motivated to provide IgM enriched plasma to increase the deposition of C3b on the microbial cells to increase the opsonization of the microbial cells and to facilitate the binding of the bi-specific or heterospecific antibodies rendered obvious by Fanger et al as evdienced by Abbas et al and Newman et al and Neilsson et al

21. Claims 21, 22, 32, 33, 34, 36-40, 43-45, 47, 49, 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanger et al as evidenced by Abbas et al and Newman et al and Neilsson et al and Vogel et al as applied to claims 21, 33, 34, 36-40, 43, 44, 47, 49 and 50 above, and further in view of Seelen et al (Immunology, 1995, Vol. 84, pp. 653-661).

Claim 22 is drawn to a method for inhibiting microbial replication in an animal, said method comprising administering to the animal a therapeutically effective amount of one or more ani-C3b(i) antibodies and one or more antibodies specific to one or more microbial antigens.

Claim 32 is drawn to a method of inhibiting septic shock in an animal comprising administering to said animal one or more anti-C3bi antibodies. Claim 45 embodies the method

of claim 32 wherein at least one of the anti-C3bi antibodies is immunospecific for C3bi linked to LPS.

The combination of Fanger et al as evidence by Abbas et al and Newman et al and Neilsson et al and Vogel et al render obvious the instant claims for the clearance of bacteria from a patient by means of bispecific of heterospecific antibodies that bind to C3b or C3bi and an effector cell antigen for the reasons set forth above. The combination of references does not specifically address the treatment of sepsis or the administration of an antibody immunospecific for one or more microbial antigens.

Seelen et al teach the administration of the human IgM antibody, HA-1A, to patients with presumed gram-negative sepsis (page 653, second column, lines 5-8). Seelen et al teach that the anti-lipid A antibody binds to rough and smooth gram negative bacteria and that binding to the "rough" gram negative organism, S minnesota, enhanced classical pathway complement fixation, deposition of C3bi on the bacterial surface and mediated binding to erythrocyte CR1 and to monocytes (page 660, first column, lines 15-23). Seelen et al teach that complement fixation, delivery to the reticulo-endothelial system or direct enhancement of opsonization contributes to the clearance of certain bacteria in the septic patient. (page 660, first column, lines 27-33).

It would have been prima facie obvious at the time the claimed invention was made to treat sepsis by the method rendered obvious in the combination of Fanger et al as evidenced by Abbas et al and Newman et al and Neilsson et al and Vogel in addition to the administration of an anti-lipid A antibody. One of skill in the art would have been motivated to do so by the teachings of Seelen et al on the enhancement of C3 deposition by the anti-lipid A antibody, E5. One of skill in the art would be motivated to increase the amount of C3bi on the surface of the bacteria in order to more efficiently target the bispecific or heterospecific antibodies of Fanger et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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